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Hippocampal volume modulates salivary oxytocin level increases after intranasal oxytocin administration

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ABSTRACT

Adverse childhood experiences have been shown to affect sensitivity to intranasal oxytocin administration, but the neural mechanisms underlying this altered sensitivity are unclear. The aim of the current study was to examine whether hippocampal abnormalities underlie the effects of adversity on the response to oxytocin administration. In a sample of healthy women (N = 54, age M = 19.63), we examined 1) the association between hippocampal volume and experiences of emotional maltreatment and 2) whether hippocampal volume reductions influence the effect of intranasal oxytocin administration on salivary oxytocin levels. There was no association between hippocampal volume and experiences of emotional maltreatment in the current study. However, we found that larger hippocampal volume was related to a stronger increase in salivary oxytocin level after intranasal oxytocin administration. The hippocampus may be a neural substrate underlying individual differences in sensitivity to oxytocin administration.

1. Introduction

Adverse childhood experiences have protracted neurobiological effects and have been associated with changes in the oxytocinergic system (Meaney, 2001). Research indicates that individuals with a history of childhood adversity show lower oxytocin levels in cerebrospinal fluid (CSF) (Heim et al., 2009), plasma (Opacka-Juffry and Mohiyeddini, 2012), and saliva (Riem et al., 2017, but see Bhandari et al., 2014), and attenuated sensitivity to intranasal oxytocin administration. For example, stress-reducing effects of intranasal oxytocin, as reflected by cortisol decreases, are impeded in individuals with a history of childhood adversity (Meinlschmidt and Heim, 2007) and in clinical groups with etiological factors rooted in childhood adversity (Bakermans-Kranenburg and Van IJzendoorn, 2013). However, the neural mechanisms underlying altered sensitivity to oxytocin administration after childhood adversity are still unclear.

One neural substrate that may underlie altered sensitivity to oxytocin administration is the hippocampus, a stress-sensitive brain region that contains high densities of oxytocin receptors (Quintana et al., 2017). The hippocampus is involved in modulating the responsiveness of the hypothalamic–pituitary–adrenal (HPA) axis to stress. However, exposure to childhood adversity results in prolonged elevated glucocorticoids that damage the hippocampus (Meaney, 2001). More specifically, early adverse experiences inhibit neurogenesis, and result in a reduced number of hippocampal neurons and decreased glucocorticoid receptor expression (McEwen et al., 2015; McGowan et al., 2009). These hippocampal changes in turn lead to impaired control of the HPA axis, which leads to hyper- or hyporesponsiveness to stress (Heim et al., 2008; McCrory et al., 2011). Indeed, research consistently shows hippocampal volume reductions and altered stress reactivity in individuals with a history of childhood adversity (Heim et al., 2008; Riem et al., 2015), which may explain why these individuals are at risk for the development of psychopathology (Heim et al., 2008).

A recent study with macaques demonstrated that early adversity also disrupts oxytocin receptor expression in the hippocampus (Baker et al., 2017). This down-modulation of the number of hippocampal oxytocin receptors may be one of the mechanisms underlying reduced sensitivity to intranasal oxytocin administration (Bakermans-Kranenburg and Van IJzendoorn, 2017). The aim of the current study was, therefore, to examine whether hippocampal abnormalities are involved in individual differences in the response to oxytocin administration. In a sample of healthy women, we examined 1) the association between hippocampal volume and experiences of emotional maltreatment and 2) whether hippocampal volume moderates the effect of

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intranasal oxytocin administration on endogenous oxytocin levels as assessed in saliva. We expected that women with a smaller hippocampus, possibly related to maltreatment, would show smaller increases in salivary oxytocin than women with a larger hippocampus and without emotional maltreatment experiences.

2. Methods

2.1. Participants

A total of 343 female undergraduate students from the Leiden University participated in the first phase of the study. In this phase, the participants completed online questionnaires on their perception of parenting experiences, including the childhood trauma questionnaire (Bernstein et al., 2003), and some demographic details. One participant was excluded due to random responses. Five females with children of their own were also excluded. One hundred eighty six students participated in the second phase of the study, which was designed to examine behavioral and cardiac responses to infant crying. Fifty-four participants with scores ranging from low to high on the childhood trauma questionnaire were selected to participate in the current magnetic resonance imaging (MRI) study. Half of the sample was randomly drawn from the participants with the 25% highest scores on the childhood trauma questionnaire and half of the sample was randomly drawn from the remaining 75%. Participants were screened for MRI contraindications, psychiatric or neurological disorders, hearing problems, pregnancy, and alcohol and drug abuse. Participants were randomly assigned to the oxytocin or the placebo condition. (n = 28 oxytocin, n = 26 placebo). The mean age of the participants was 19.63 years (SD = 1.43, range 18–27). 72.2% of the participants used oral contraceptives. Permission for this study was obtained from the Ethics Committees of the Institute of Education and Child Studies of Leiden University and of the Leiden University Medical Centre.

2.2. Procedure

Participants were invited for an MRI study preferably in the luteal phase of their menstrual cycle in order to control for influences of menstrual cycle. During the luteal phase, plasma oxytocin levels are lower (Salonia et al., 2005) and more responsive to stimulation such as by nipple stimulation (Leake et al., 1984). Women were asked about the date of their last menstruation and this information was used to schedule the lab session. Menstrual phase and use of oral contraceptives were balanced across the placebo and oxytocin group: 23 participants in the oxytocin and 22 participants in the placebo group were in the luteal phase, whereas 4 participants in the oxytocin group and 3 participants in the placebo group were in the follicular phase. 21 participants in the oxytocin group and 18 participants in the placebo group used oral contraceptives. For two participants it was not possible to determine menstrual phase, because of use of hormonal intrauterine device. They were instructed to abstain from alcohol and excessive physical activity during the 24 h before the start of study, and from caffeine on the data collection day. The session started with the administration of a mood questionnaire and saliva collection to assess baseline oxytocin levels. Afterwards, participants took 6 puffs of nasal spray containing oxytocin (16 IU total) or 6 puffs of a placebo spray under supervision of the experimenter. Effects of 16 IU of oxytocin have been reported in previous studies (Riem et al., 2011; Van IJzendoorn et al., 2012). A previous study indicated no difference in salivary oxytocin level increases after 16 or 24 IU oxytocin administration (Van IJzendoorn et al., 2012). Drug administration was double-blind. Approximately 35 min after nasal spray administration, a structural MRI scan and functional scans were acquired during several paradigms. Approximately 75 min after nasal spray administration, a second saliva sample was collected.

2.3. Mood

Mood was measured with the Positive Affect Negative Affect questionnaire (PANAS; see Supplemental Material).

2.4. Childhood trauma questionnaire

Participants completed the Dutch version of the Childhood Trauma Questionnaire Short Form (CTQ-SF, Bernstein et al., 2003). CTQ-SF is a measure of self-reported experiences of childhood abuse. Twenty-eight items were used to assess experiences of physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect. Each item (e.g., “During my childhood I felt hated by family”) was rated on a 5-point Likert scale ranging from never true to very often true. In the current study we focused on the emotional abuse and emotional neglect subscales because several studies with similar samples have shown that experiences of emotional maltreatment are associated with dysregulations of the oxytocin system (Riem et al., 2017; Van Ijzendoorn et al., 2011). Moreover, sexual abuse is rather rare compared to emotional maltreatment (Euser et al., 2013). The selection of participants was based on these subscales, which therefore showed largest variability in the current sample (see Table S1 for the means scores on each CTQ subscale). An emotional maltreatment scale was created (α = .81) by averaging the 10 items tapping into the emotional abuse and emotional neglect dimensions. The mean score was 1.75 (SD = 0.69) with scores ranging from 1 to 4.40. A log transformation was applied to the emotional maltreatment variable to approach a normal distribution.

2.5. Salivary oxytocin

At least 1 ml of unstimulated saliva was collected into cryotubes for each sample using the passive drool method. Samples were immediately frozen and were stored at -20 °C until batch assay. Level of oxytocin in saliva was assayed using the commercially available EIA kit as per the method previously described and used before (see Supplemental Material). Prior to the enzyme immunoassay procedure, in keeping with the manufacturer’s strong recommendation, an extraction step was performed based on instructions accompanying the EIA kit available in February 2011 (ADI-900-153, Enzo Life Science, Plymouth Meeting, PA, USA).

2.6. MRI data acquisition and analysis

Scanning was performed with a standard whole-head coil on a 3-T Philips Achieva TX MRI system (Philips Medical Systems, Best, the Netherlands) in the Leiden University Medical Center. A T1-weighted anatomical scan was acquired (flip angle = 8°, 140 slices, voxel size 0.875 × 0.875 x 1.2 mm). Volumes of the left and right hippocampus were assessed using FIRST, part of FSL FMRIB’s Software Library, http://www.FMRIb.ox.ac.uk/fsl (see Supplemental Material). Hippocampal volumes were extracted after affine registration to standard space and subcortical structure segmentation. Registrations and segmentations were visually inspected, and no errors were observed. After hippocampal volume extraction, the fslstats command was used to assess volumes of the left and right hippocampus. The number of voxels and mm^3 of left and right hippocampus were obtained using the threshold options to select out the single label numbers corresponding to the left and right hippocampus (see https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST/UserGuide). Volumes of the left and right hippocampus and total brain volume (mm^3) (see Supplemental Material) were exported to SPSS.

2.7. Statistical analyses

A Repeated Measures ANOVA was performed with salivary oxytocin as dependent variable, time (before and 75 min after administration) as

within-subject factor, group (oxytocin, placebo) as between-subject factor and mean (left/right) hippocampal volume as covariate. Whole brain volume, mood, time between nasal spray administration and second saliva collection, oral contraceptive use, and menstrual cycle (luteal, follicular) were entered as additional covariates in the analyses. Another Repeated Measures ANOVA was performed, again with salivary oxytocin as dependent variable, time as within-subject factor and group as between-subject factor, but with emotional maltreatment as covariate. Mood, time between nasal spray administration and second saliva collection, oral contraceptive use, and menstrual cycle (luteal, follicular) were entered as additional covariates in the analyses.

3. Results

Correlational analysis showed that mean hippocampal volume was not significantly related to emotional maltreatment (r = .01, p = .95) or baseline oxytocin levels (r = .02, p = .92). Neither was there a significant correlation between emotional maltreatment and baseline oxytocin levels (r = -0.10, p = .48). The repeated measures ANOVA with salivary oxytocin levels as dependent variable showed significant main effects of time (F(1,44) = 9.78, p = .003, partial η^2 = 0.18), hippocampal volume (F(144) = 6.68, p = .013, partial η^2 = 0.13), and group (oxytocin, placebo) (F(1,44) = 4.05, p = .050, partial η^2 = 0.08). In addition, there was a significant time x group interaction (F(1,44) = 4.11, p= .049, partial η^2 = 0.09) and a significant time x group x hippocampal volume (continuous) three-way interaction (F(1,44) = 6.09, p = .018, partial η^2 = 0.12), indicating that the increase in oxytocin levels after oxytocin administration was different for individuals with a smaller versus larger hippocampus. Hippocampal volume was then dichotomized using a median-split (median = 3876.67) in order to interpret the three-way interaction. Fig. 1 shows that individuals with a larger hippocampus showed a greater increase in salivary oxytocin after oxytocin administration than individuals with a smaller hippocampus. Mean oxytocin levels before and after oxytocin/placebo administration are presented in Table 1. The interaction between hippocampal volume, oxytocin/placebo group and time remained significant when age was included as an additional covariate (F(1,43) = 6.13, p = .017, partial η^2 = 0.13). The repeated measures ANOVA with childhood emotional maltreatment as covariate did not show a significant main effect of emotional maltreatment on salivary oxytocin (F(1,45) = 1.07, p = .306, partial η^2 = 0.02). Neither was there a significant time x group x maltreatment three-way interaction (F(1,45) = 1.31, p = .259, partial η^2 = 0.03). The analyses were repeated with the total score on the childhood trauma questionnaire, but the results not did change (see supplemental material). Following a reviewer suggestion, analyses were repeated separately for left and right hippocampal volume in order to explore lateralization effects, but there were none. The time x group x maltreatment three-way interaction was marginally significant for both hemispheres (left: F(1,45) = 3.69, p = .061, partial η^2 = 0.08; right: F(1,45) = 3.48, p = .069, partial η^2 = 0.07.

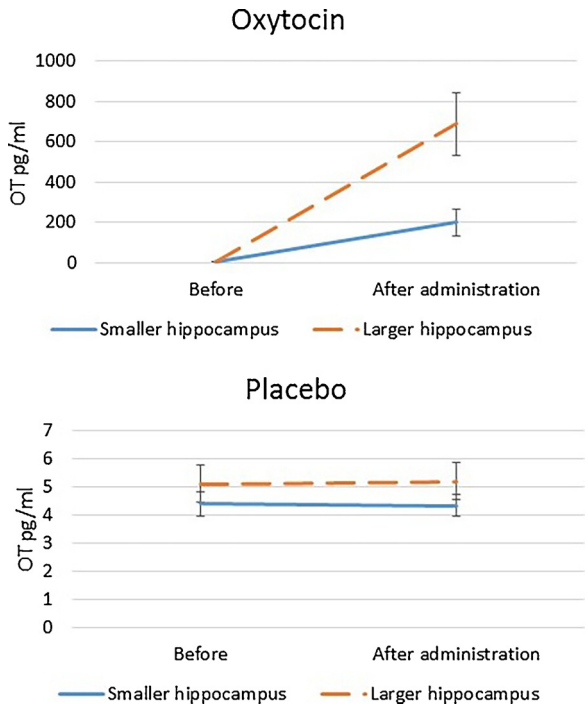

Fig. 1. Mean (SE) oxytocin levels (pg/ml) before and after administration of the oxytocin (upper panel) and placebo (lower panel) nasal spray for individuals with a smaller (oxytocin N = 14, placebo N = 13) and a larger hippocampus (oxytocin N = 14, placebo N = 13). For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.

Table 1
Mean (SD) oxytocin levels (pg/ml) before and after administration of the oxytocin and placebo nasal spray for individuals with a smaller (oxytocin N = 14, placebo N = 13) and a larger hippocampus (oxytocin N = 14, placebo N = 13).

		Before administration		After administration	
		M	SD	M	SD
Oxytocin	Smaller hippocampus	5.21	2.21	200.23	241.28
	Larger hippocampus	5.18	2.35	689.64	581.78
Placebo	Smaller hippocampus	4.40	1.54	4.33	1.36
	Larger hippocampus	5.12	2.42	5.21	2.44

4. Discussion

The current study shows that hippocampal volume is associated with sensitivity to intranasal oxytocin administration. We found that larger hippocampal volume was related to a stronger increase in salivary oxytocin level after intranasal oxytocin administration. Our study is the first to demonstrate that effects of intranasal oxytocin may be dependent on hippocampal structure. The results are in line with those of a previous study showing that hippocampal functional connectivity plays a role in individual differences in sensitivity to intranasal oxytocin (Fan et al., 2014). The hippocampus seems to be an important neural moderator in the effects of oxytocin, possibly because it contains a high number of oxytocin receptors (Quintana et al., 2017). As a result, variations in hippocampal structure may influence endogenous oxytocin level increases after intranasal oxytocin administration.

A question that should be addressed in future research is *how* hippocampal structure modulates the response to intranasal oxytocin. One of our hypotheses is that hippocampal neuronal loss after childhood adversity underlies reduced sensitivity to oxytocin administration in individuals with adverse experiences. Another hypothesis is that epigenetic changes after childhood adversity result in reductions in oxytocin receptor expression and influence sensitivity to intranasal oxytocin. Adverse experiences stimulate vasopressin release and this may lead to increased vasopressin receptor density and reduced oxytocin receptor density and, thus, an imbalance between the oxytocin and vasopressin system (Bakermans-Kranenburg and Van IJzendoorn, 2017). Hippocampal neuronal loss and reductions in oxytocin receptor expression after childhood adversity may in turn impede the feedforward mechanism of the oxytocinergic system (Van IJzendoorn et al., 2012; Churchland and Winkielman, 2012), with more production and release of endogenous oxytocin with increased oxytocin levels after

administration, which may result in more short-lived oxytocin effects or even the absence of an effect.

In the current study, experiences of emotional maltreatment did not moderate the effects of oxytocin. Neither was there an association between hippocampal volume and emotional maltreatment, perhaps because our sample consisted of healthy women without or with only moderate experiences of emotional maltreatment, which is a limitation of the study, or because the hippocampus underlies general individual variability in oxytocin sensitivity, not necessarily dependent on maltreatment. Future studies should therefore examine neural moderators of the effects of oxytocin in clinical or maltreated samples, taking into account different types of maltreatment and, on the other hand, the potentially protective role of positive parenting experiences (Luby et al., 2012). Studying neural mechanisms underlying individual differences in the response to oxytocin may shed more light on oxytocin's therapeutic potential, as it has been suggested to be only effective in (clinical) groups without adverse childhood experiences (Bakermans-Kranenburg and Van IJzendoorn, 2013; Van IJzendoorn and Bakermans-Kranenburg, 2016). In addition, future research should examine effects of repeated intranasal oxytocin on endogenous oxytocin levels and effects up to a longer period of time after administration because effects of adversity may increase with time passed since administration. Another limitation that should be noted is the use of self-reported date of last menstruation to determine menstrual phase. Furthermore, as it is still unclear how and whether intranasal oxytocin enters the central nervous system, future studies should examine the possible pathways through which oxytocin may reach the hippocampus and other brain regions. A recent study with nonhuman primates showed that intranasally administered oxytocin penetrates CSF, possibly via a direct pathway from the nasal cavity via the trigeminal or olfactory nerves to CSF, although an indirect intranasal oxytocin delivery across the blood-brain barrier might also be possible (Lee et al.,2018).

5. Conclusions

In conclusion, our study is the first to suggest that hippocampal volume modulates salivary oxytocin level increases after intranasal oxytocin administration and indicates that the hippocampus is a potential neural substrate underlying individual differences in sensitivity to oxytocin administration.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2018.11.015.

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